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# HEAT EXCHANGE AFTER ATROPINE AND PRALIDOXIME ADMINISTRATION

U S ARMY RESEARCH INSTITUTE  
OF  
ENVIRONMENTAL MEDICINE  
Natick, Massachusetts

DECEMBER 1986

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<p>This report summarizes a tightly controlled laboratory study in which the effects of intra-muscular saline (control), atropine (2 mg), and/or pralidoxime (600 mg) on heat exchange were evaluated in four healthy males during seated, cycle exercise (55% <math>\dot{V}O_2</math> peak) in a temperate environment (<math>T_a = 30.3^\circ\text{C}</math>, <math>P_w = 1.0</math> kPa). Esophageal (<math>T_{es}</math>), rectal (<math>T_{re}</math>), and mean skin temperature (<math>T_{sk}</math>), and chest and forearm sweating (<math>\dot{m}_{fs}</math>) were continuously measured. Skin blood flow (FBF) from the forearm was measured twice each minute by venous occlusion plethysmography. Whole body sweating was calculated from weight changes. The expected result of atropine injection, decreased eccrine sweating (<math>-60\%</math>, <math>p &lt; 0.05</math>) and elevated esophageal (<math>+0.4^\circ</math>, <math>p &lt; 0.05</math>) and skin temperatures (<math>+2.1^\circ\text{C}</math>, <math>p &lt; 0.05</math>) was observed relative to control. Heart rate (<math>+22 \text{ b}\cdot\text{min}^{-1}</math>) and FBF (<math>+9 \text{ ml}\cdot 100\text{cc}^{-1}\cdot\text{min}^{-1}</math>) were higher after atropine. Pralidoxime, in general, did not affect the core and skin temperature responses to the exercise differently from control; however, a slightly elevated FBF (<math>+3 \text{ ml}\cdot 100\text{cc}^{-1}\cdot\text{min}^{-1}</math>, <math>33\%</math>) compensated for the reduction in whole body sweating (<math>-45\%</math>, <math>p &lt; 0.05</math>) that we observed. The combination of the</p>					
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drugs resulted in significantly higher esophageal ( $0.4^{\circ}\text{C}$ ) and skin ( $0.9^{\circ}\text{C}$ ) temperatures than atropine alone, as has been previously shown. The thermoregulatory disadvantage of inhibited sweating by atropine was partially compensated for by enhanced skin blood flow in this environment where  $T_{\text{sk}}$  was higher. Pralidoxime was shown to decrease whole body sweating by a mechanism as yet unexplained.

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HEAT EXCHANGE AFTER ATROPINE AND PRALIDOXIME ADMINISTRATION

by

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## PREFACE

The methodology and findings of these studies as described (and referenced) in this report have been published in or submitted to the open literature as follows:

Kolka, M.A., L.A. Stephenson, S.P. Bruttig, B.S. Cadarette and R.R. Gonzalez. Human Thermoregulation after atropine and/or pralidoxime administration. Aviat. Space & Environ. Med. (In Press) 1987.

Stephenson, L.A. and M.A. Kolka. Exercise after atropine and pralidoxime increases the rational effective temperature. (Submitted for publication).

Kolka, M.A., L.A. Stephenson, S.P. Bruttig and R.R. Gonzalez. Systemic atropine augments cutaneous blood flow in thermoregulation. (Submitted for publication).

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## ABSTRACT

This report summarizes a tightly controlled laboratory study in which the effects of intramuscular saline (control), atropine (2 mg), and/or pralidoxime (600 mg) on heat exchange were evaluated in four healthy males during seated, cycle exercise (55%  $\dot{V}O_2$  peak) in a temperate environment ( $T_a = 30.3^\circ\text{C}$ ,  $P_w = 1.0$  kPa). Esophageal ( $T_{es}$ ), rectal ( $T_{re}$ ), and mean skin temperatures ( $\bar{T}_{sk}$ ), and chest and forearm sweating ( $\dot{m}_s$ ) were continuously measured. Skin blood flow (FBF) from the forearm was measured twice each minute by venous occlusion plethysmography. Whole body sweating was calculated from weight changes. The expected result of atropine injection, decreased eccrine sweating (-60%,  $p < 0.05$ ) and elevated esophageal ( $+0.4^\circ\text{C}$ ,  $p < 0.05$ ) and skin temperatures ( $+2.1^\circ\text{C}$ ,  $p < 0.05$ ) was observed relative to control. Heart rate ( $+28 \text{ b} \cdot \text{min}^{-1}$ ) and FBF ( $+9 \text{ ml} \cdot 100\text{cc}^{-1} \cdot \text{min}^{-1}$ ) were higher after atropine. Pralidoxime, in general, did not affect the core and skin temperature responses to the exercise differently from control; however, a slightly elevated FBF ( $+3 \text{ ml} \cdot 100\text{cc}^{-1} \cdot \text{min}^{-1}$ , 33%) compensated for the reduction in whole body sweating (-45%,  $p < 0.05$ ) that we observed. The combination of the drugs resulted in significantly higher esophageal ( $0.4^\circ\text{C}$ ) and skin ( $0.9^\circ\text{C}$ ) temperatures than atropine alone, as has been previously shown. The thermoregulatory disadvantage of inhibited sweating by atropine was partially compensated for by enhanced skin blood flow in this environment where  $T_a < \bar{T}_{sk}$ . Pralidoxime was shown to decrease whole body sweating by a mechanism as yet unexplained.

Key Words: atropine sulfate, core temperature, cutaneous blood flow, exercise in the heat, pralidoxime chloride, sweating rate

## INTRODUCTION

Eccrine sweat gland activity is depressed by systemic or local atropine administration through competitive inhibition of cholinergic receptors (1,9,14) resulting in reduced evaporative heat loss (40-60%) in adult males (1,9,13). A cutaneous "atropine flush" accompanies these inhibitory effects on the sweat gland (4), but whether the "flush" is an active mode of heat exchange has not been elucidated. We (5) and others (3) have estimated higher cutaneous blood flow after atropine by calculating enhanced dry heat loss. However, the measurement of cutaneous blood flow by venous occlusion plethysmography or other methods after whole body atropine administration has not been undertaken.

Pralidoxime chloride (2PAM) is currently used as an antidote to organophosphate poisoning. The action of 2PAM centers around the reactivation of bound acetylcholinesterase for the hydrolysis of acetylcholine to enable synapses to function normally (6). In the absence of impaired enzyme, the action of 2PAM is not clear. When given in therapeutic doses (600 mg, i.m.), 2PAM caused no changes in core temperature, skin temperature, heart rate or whole body sweating rate in resting men at 40.5°C, 1.5 kPa (13). After oral 2PAM administration (2), there were no changes in core or skin temperature during low intensity exercise at 19, 29, 38 or 46°C. However, whole body sweating was reduced an average of 10% in these studies. Transient hypertension occurs following 2PAM treatment (6), and in the presence of a higher sympathetic drive (exercise or combat), sudden and dramatic increases in precapillary vascular resistance (therefore elevating blood pressure) may occur in individuals treated with pralidoxime chloride with appropriate changes in peripheral blood flow and heat dissipation. Additionally, systemic

administration of 2PAM and atropine point to an augmentation of the atropine induced rise in body temperature in the presence of 2PAM (2).

→ In the present study, we were interested in ascertaining the individual and combined actions of atropine and pralidoxime on thermoregulatory sweating and vasodilation in healthy males during moderate intensity exercise in a temperate environment. — cont'd on DD 1473

#### Military Relevance

The U.S. Army must be prepared to engage in military operations under varied environmental conditions. During these operations, soldiers will engage in a variety of tasks involving physical exercise. It is well established that there are exercise performance decrements in hot compared to thermal neutral environments. Furthermore, if a chemical agent were to be introduced into a hot environment, either the use of protective clothing (MOPP) or a pharmaceutical antidote (such as atropine) would result in further performance decrements.

This study was designed to expand our data base on the physiological effects of atropine and pralidoxime administration in the absence of organophosphate nerve agent. Specifically, an evaluation of peripheral blood flow after atropine and pralidoxime was evaluated.

### Minimizing Risk to Subjects

Except for the intramuscular administration of atropine and pralidoxime, the procedures in this study fell within the framework, restrictions and safety limitations of the Type Protocols for: Human Research Studies of Thermal stress; and Exercise and Physical Training (Mar 1984\*).

To minimize risks associated with atropine and pralidoxime, volunteers were given medical examinations prior to acceptance as subjects. No one with a history of asthma, glaucoma or intraocular injury, peptic ulcer, or adverse reactions to previous atropine administration (as in the form of eye drops, antispasmodics or decongestants) was used as a subject. Fatalities from atropine alone are rare; the lethal dose is unknown (It may be as low as 65 mg for some individuals, or greater than 1000 mg for others). Central nervous system manifestations (emotional instability, anxiety, hallucinations, etc.) are usually absent or mild with less than 5 mg dosages. Fatigue, headache, lightheadedness and non-coordinated movement can be expected in at least 25% of subjects receiving a 2-mg dosage. Responses from injection of pralidoxime chloride (600 mg) are difficult to differentiate from the effects of atropine or organophosphate compounds that are usually in the system at the same time. These responses include dizziness, blurred vision, diplopia, headache, drowsiness, nausea, tachycardia, hyperventilation, and muscular weakness. In general, pralidoxime chloride administered by itself intramuscularly results in the soreness of the area of injection.

\*Approved 5 March 1984. The Type Protocol provides information and explanations about conditions, standards and safeguards, in order to serve as an encompassing framework for specific in-house studies in its general subject area. It is to be used as a reference to facilitate the understanding and review of specific study protocols which conform to its provisions, and thus do not exceed the degree of risk, and safety limits herein stipulated (reference para 19, USAMRDC Reg 70-25, 27 April 1981).

## METHODS AND RESULTS

### Methods

Subjects. Four fit males ( $\dot{V}O_2$  peak =  $46 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) volunteered for the study following consent procedures passed by our local Human Use Committee. They had an average ( $\pm$  SD) age of  $21 \pm 2$  yrs, height of  $182 \pm 9.1$  cm, weight of  $81.3 \pm 9.8$  kg, DuBois surface area of  $2.03 \pm .16 \text{ m}^2$ , percentage of body fat (hydrostatic weighing) of  $18.7 \pm 4.4\%$  and a lean body mass of  $66.1 \pm 3.6$  kg.

Protocol. Testing occurred during November 1985. All subjects were familiarized with all testing and measurement procedures before data collection began. Subjects were tested on four separate days in an ambient temperature of  $30^\circ\text{C}$  with an ambient water vapor pressure ( $P_w$ ) =  $1.0 \text{ kPa}$ . Testing occurred after sterile saline, injection (im), after 2 mg of atropine sulfate (Elkin-Sinn, Cherry Hill, NJ), after 600 mg pralidoxime chloride (Protopam chloride, Ayerst, NY, NY) or following 2 mg atropine plus 600 mg pralidoxime chloride. Subjects were not aware of the drug(s) being injected. Test days were separated by 48 hours, and the order of drug presentation was counterbalanced. Experiments were conducted between 0700 and 1000h, with any one subject tested at the same time each day to control for circadian variation in heat loss responses (15). Subjects had fasted 12 hours before testing.

Physiological variables. The seated exercise level was 55% of a previously determined  $\dot{V}O_2$  peak on a modified cycle ergometer (11). Total exposure time was 80 minutes, which included a 5-min base line period after instrumentation and equilibration, the injection of the appropriate drug, 30

minutes of rest, 30 minutes of submaximal exercise and a 15-minute recovery period. We continuously recorded esophageal temperature ( $T_{es}$ ), rectal temperature ( $T_{re}$ ), an eight site, mean weighted skin temperature ( $\bar{T}_{sk}$ ) (12), and sweating rate (7) from the chest ( $\dot{m}_{sch}$ ) and forearm ( $\dot{m}_{sa}$ ). Heart rate (HR), measured from the electrocardiogram, and blood pressure (automatic auscultation) were measured each 2.5 min. Forearm blood flow (FBF) was measured twice each min by venous occlusion plethysmography (8,16) on the contralateral forearm from which blood pressure was measured. Metabolic heat production was estimated by open circuit spirometry at 15 minutes of rest, 10 minutes of exercise, 25 minutes of exercise and at 5 minutes of recovery. Total body sweating rate ( $\text{g}\cdot\text{min}^{-1}$ ) was determined by pre- and post-experiment weights of the nude body.

**Statistical Analysis.** Analysis of variance routines were used to compare all variables at the time of the metabolic heat production measurements (rest, 10 and 25 minutes of exercise, and 5 minutes of recovery). Regression equations of both internal temperature measurements over time were generated to calculate the rate of change in heat content. Tukey's test of critical differences was used where appropriate. All differences are reported at  $P < 0.05$ , unless otherwise noted.

### Results

There were no statistically significant differences in any of the resting variables for any of the four drug treatments. Furthermore, there was no treatment effect on the metabolic heat production or mean arterial pressure during exercise which averaged  $351 \text{ W}\cdot\text{m}^{-2}$  and 104 Torr, respectively. Mean heat exchange information is presented in Table 1 for the four subjects under all testing conditions. As expected, atropine elevated heart rates during

exercise (22%) and recovery (62%) over those rates seen in control experiments with pralidoxime not affecting exercise heart rate. The combination of atropine and pralidoxime increased exercise (19%) and recovery (80%) heart rates. Depressed local and whole body sweating (arm, -64%; chest, -77%; whole body, -58%) occurred with atropine as did the expected rise in both core and mean weighted skin temperatures. FBF was elevated following atropine; 83% during exercise and 170% during recovery. Pralidoxime injection, in general, did not affect rest, exercise or recovery values for  $T_{re}$ ,  $T_{es}$ , or  $\bar{T}_{sk}$ . However, FBF was slightly elevated ( $+3.0 \text{ ml} \cdot 100\text{cc}^{-1} \cdot \text{min}^{-1}$ ; 33%, NS), and whole body sweating ( $-6.2 \text{ g} \cdot \text{min}^{-1}$ ; -47%) and recovery chest sweating ( $0.48 \text{ mg} \cdot \text{cm}^{-2} \cdot \text{min}^{-1}$ ) were reduced. The combination of atropine and pralidoxime resulted in higher  $T_{es}$  ( $0.4^{\circ}\text{C}$ ) and  $\bar{T}_{sk}$  ( $0.7^{\circ}\text{C}$ ) than atropine itself by the 25th minute of exercise. FBF, whole body and local sweating were not different from the atropine treatment. These results are graphically presented in Figure 1.

The rate of increase ( $dT/dt$ ) for esophageal and rectal temperature is shown in Table 2 for all subjects during all treatments. As expected,  $dT_{es}/dt$  was higher than  $dT_{re}/dt$  in all cases. In addition,  $dT_{es}/dt$  was significantly affected by all treatments, whereas  $dT_{re}/dt$  was affected only by the combination of drugs.

Table 1. Mean ( $\pm$ SD) temperature parameters for the four subjects during the four treatments at rest, during exercise and recovery.

Saline	$T_{es}$ (°C)	$T_{re}$ (°C)	$T_{sk}$ (°C)	FBF (ml $\cdot$ 100cc $^{-1}\cdot$ min $^{-1}$ )	Arm $\dot{m}_s$ (mg $\cdot$ cm $^{-2}\cdot$ min $^{-1}$ )	Chest $\dot{m}_s$ (mg $\cdot$ cm $^{-2}\cdot$ min $^{-1}$ )	$\dot{M}_s$ (g $\cdot$ min $^{-1}$ )	Heart Rate (b $\cdot$ min $^{-1}$ )
Rest	36.67(.15)	37.17(.25)	34.04(.28)	1.84(.83)	.16(.06)	.31(.35)		67(8)
Exercise 1	37.15(.14)	37.27(.22)	33.32(.59)	6.09(.87)	.97(.17)	1.43(.31)		127(4)
Exercise 2	37.37(.15)	37.64(.15)	33.62(.51)	9.21(.42)	1.08(.30)	1.78(.61)		130(5)
Recovery	37.01(.36)	37.76(.16)	33.64(.50)	5.55(.76)	.74(.38)	1.78(.87)	13.23(3.68)	87(10)
<u>Atropine</u>								
Rest	36.61(.20)	37.06(.20)	34.06(.30)	1.84(.45)	.15(.04)	.23(.28)		59(13)
Exercise 1	37.08(.18)	37.13(.15)	34.92(.48)*	11.04(3.08)*	.35(.20)*	.33(.34)*		146(11)*
Exercise 2	37.78(.18)*	37.62(.14)	35.72(.49)*	17.08(5.78)	.43(.14)*	.61(.28)*		158(4)*
Recovery	37.80(.22)	37.97(.11)	36.03(.35)*	15.04(8.01)*	.45(.17)*	.67(.36)*	5.53(1.37)*	142(13)*
<u>Pralidoxime</u>								
Rest	36.48(.30)	36.92(.28)	33.97(.54)	1.93(.94)	.12(.01)	.12(.02)		66(12)
Exercise 1	37.00(.29)	37.14(.25)	33.76(.54)*#	9.13(4.13)	1.14(.32)	1.47(.33)		126(11)
Exercise 2	37.16(.25)#	37.56(.22)	33.95(.80)#	12.26(4.20)#	1.41(.21)*	1.67(.39)		123(12)
Recovery	36.98(.21)#	37.66(.19)	33.80(.73)#	5.34(1.82)#	.72(.43)	1.44(.80)*	7.03(2.16)*	93(23)
<u>Combination</u>								
Rest	36.76(.28)	37.11(.23)	33.97(.64)	1.35(.29)	.16(.04)	.34(.30)		71(11)
Exercise 1	37.32(.25)	37.24(.20)	35.34(.65)*#+	12.64(1.74)*	.35(.24)	.26(.14)		139(6)*
Exercise 2	38.18(.27)*#+	37.83(.28)	36.40(.57)*#+	17.36(4.63)*+	.45(.18)	.45(.16)*		155(2)*
Recovery	38.28(.21)*#+	38.29(.27)	36.71(.29)*#+	16.31(2.12)*+	.40(.21)*	.95(.30)*	5.35(2.91)*	157(14)*

\*Different from saline ( $p < 0.05$ )

#Different from atropine ( $p < 0.05$ )

+Different from pralidoxime ( $p < 0.05$ )

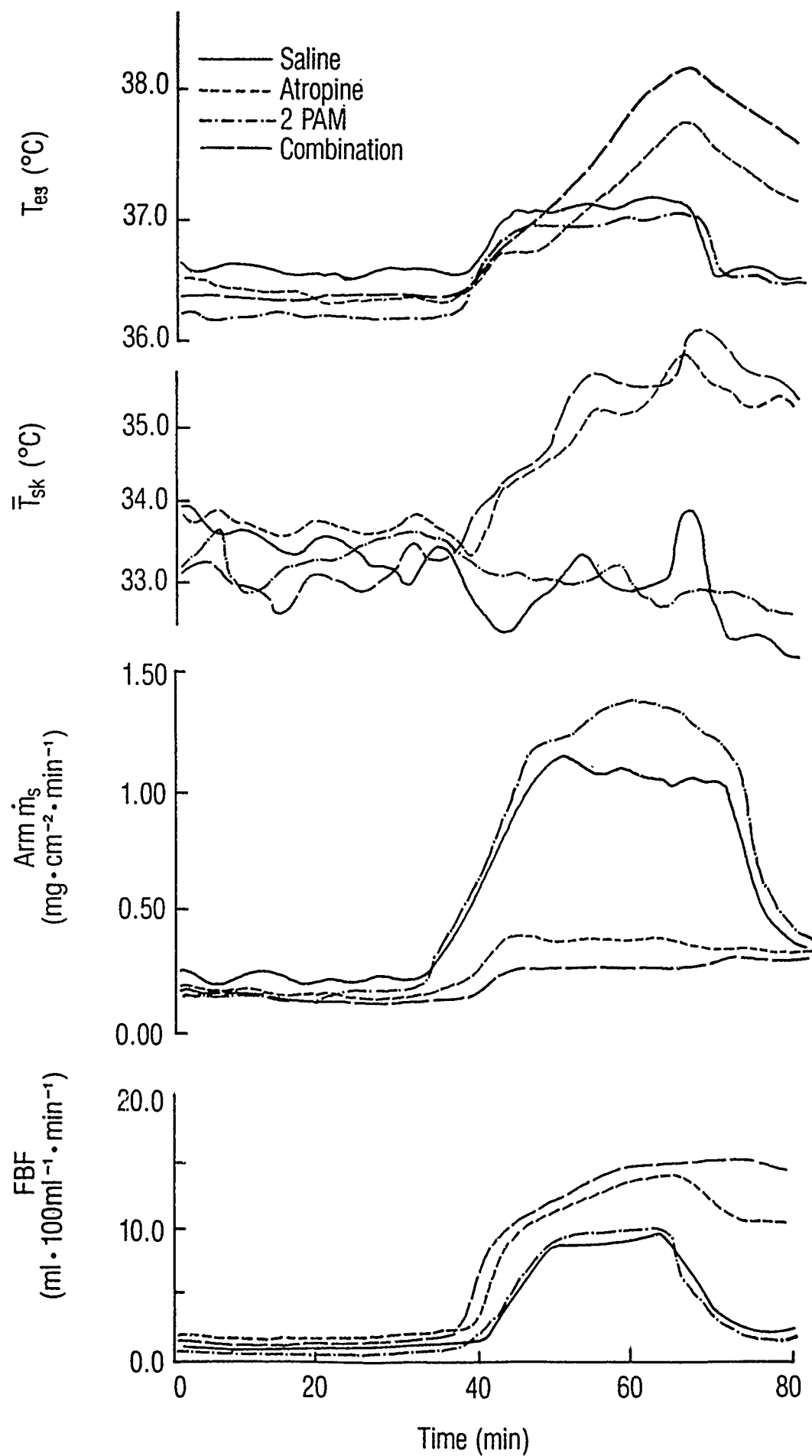


Table 2. Individual and mean ( $\pm$ SD)  $dT/dt$  ( $^{\circ}\text{C}\cdot\text{min}^{-1}$ ) for esophageal and rectal temperatures during exercise transients for the four treatments

<u>Saline</u>	<u>Esophageal</u>	<u>Rectal</u>
S <sub>1</sub>	.08779	.04060
S <sub>2</sub>	.09360	.02349
S <sub>3</sub>	.06250	.02232
S <sub>4</sub>	.06823	.01899
	<u>.0781</u> (.0150)	<u>.0264</u> (.0097)
 <u>Atropine</u>		
S <sub>1</sub>	.07400	.04059
S <sub>2</sub>	.07669	.02273
S <sub>3</sub>	.05310	.02810
S <sub>4</sub>	.0604	.03111
	<u>.0660</u> (.0112)*	<u>.0306</u> (.0075)
 <u>Pralidoxime</u>		
S <sub>1</sub>	.07909	.05701
S <sub>2</sub>	.10814	.03067
S <sub>3</sub>	.08648	.02030
S <sub>4</sub>	.08187	.02423
	<u>.0889</u> (.0132)*#	<u>.0331</u> (.0165)
 <u>Combination</u>		
S <sub>1</sub>	.08605	.04387
S <sub>2</sub>	.06235	.04336
S <sub>3</sub>	.05352	.03851
S <sub>4</sub>	.05195	.03707
	<u>.0635</u> (.0157)*+	<u>.0407</u> (.0034)*#+

S<sub>1</sub> through S<sub>4</sub> are subject numbers.

\*Different from saline ( $p < 0.05$ )

#Different from atropine ( $p < 0.05$ )

+Different from pralidoxime ( $p < 0.05$ )

## DISCUSSION

This investigation provides initial evidence that systemic atropine administration alters peripheral heat loss, not only via depressed thermoregulatory sweating, but also through elevated skin blood flow. Additionally, pralidoxime administration results in a depressed whole body sweating response without affecting core and skin temperature regulation in a temperate environment during moderate intensity exercise. The combination of the two drugs, in general, confirms the potentiation of impaired heat exchange that has been reported previously (2).

The depression in thermoregulatory sweating seen following atropine was expected (1,9), and was of the same magnitude as previously reported for unacclimated subjects (9). The compensation for reduced evaporative heat loss from the skin, which occurs via skin blood flow has been suggested (3,5) and may in part explain the atropine flush which is usually observed. (4) This elevation in skin blood flow appears to be a result of an enhanced sensitivity to the increasing esophageal temperature drive (10).

The responses of the subjects after the pralidoxime injection were not completely expected. One response which appears equivocal is the depression in whole body sweating (Table 2). Smaller decreases in whole body sweating were demonstrated previously (2), but no record of this level of inhibition is available. Paradoxically, local sweating was not depressed by the pralidoxime treatment, perhaps indicating a differential effect of the inhibition of sweat secretion at different locations. Since  $T_{es}$  and  $\bar{T}_{sk}$  were not different after pralidoxime injection compared to saline treatment (Table 2), the slight enhancement in FBF resulting in further sensible heat loss together with the regulatory sweating observed was sufficient for whole body heat dissipation.

In environments where  $T_a > \bar{T}_{sk}$ , heat dissipation would be compromised during pralidoxime treatment due to inhibited sensible heat exchange by the environmental gradient as well as by inhibited evaporation. The enhancement in skin blood flow is contrary to what we expected, since transiently increased vascular resistance has been seen after pralidoxime (6), which would result in unchanged or lower skin blood flow.

Atropine given in combination with pralidoxime (separate injections, same time frame) resulted in elevated  $T_{es}$  and  $\bar{T}_{sk}$  by the 25th minute of exercise (Table 1), with a decrease in whole body and local sweating. The responses in  $T_{es}$  and  $\bar{T}_{sk}$  were significantly augmented in this time frame, over those seen with atropine alone, implying a synergistic effect of the two drug actions (2). Chest and whole body sweating were slightly lower in the combined experiments, while FBF was not different from atropine treatment, which resulted in the elevated core and surface temperatures observed. Again, if the thermal gradient from the environment to the body surface is reversed, as in the case where  $T_a > \bar{T}_{sk}$ , this potentiation of atropine effects with 2PAM would increase the heat strain on the individual and affect performance.

We have demonstrated that atropine affects the cutaneous perfusion (arm site) as well as peripherally inhibiting eccrine (cholinergic) sweating. Specifically, FBF is enhanced with atropine, and this avenue partially compensates for the sweating inhibition evident in this relatively cool environment. Pralidoxime, on the other hand, appears to also inhibit sweating and increase FBF, albeit to a much lesser extent than atropine. The regulation of internal core temperature ( $T_{es}$ ) with 2PAM is not radically affected in comparison to control experiments for the dosage and environmental conditions of this study, although the rate of heat loading is enhanced (Table

2). It would be interesting to study and determine if this is the case in an environment where the gradient between ambient temperature and  $\bar{T}_{sk}$ , (e.g.,  $T_a - \bar{T}_{sk}$ ) is small or when ambient temperature actually exceeds skin temperature. Finally, the combination of atropine and pralidoxime resulted in elevated heat storage during exercise, pointing to the possibility of heat injury in more severe environmental conditions.

#### SUMMARY

In summary, observations from this study were:

- 1) The expected decline in local and whole body sweating followed atropine treatment.
- 2) Pralidoxime, by itself, depressed whole body sweating.
- 3) The combination of drugs resulted in greater increases in core and surface temperatures than either drug used alone.

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